

REMARKS

Claims 1-2, 22, 25, and 31-39 are presently pending. Claim 33 has been rewritten from a dependent to an independent form. No new matter has been added.

On May 6, 2004, Applicants' representative Kathleen Petrillo and Examiner Shailendra Kumar had a scheduled telephone interview to discuss the patentability of claims 1-2, 22, 25, and 31-39. The Examiner noted that amending claim 1 to include sulfur-containing benzamidozole compounds instead of sulfur-containing compounds would overcome the 35 U.S.C. § 112 rejection. Applicant notes that claim 33 has been so amended. No conclusion was reached regarding 35 U.S.C. § 102 and 103 rejections. Instead, the Examiner requested that Applicants submit proposed amendments and remarks in written form for consideration.

I. 35 U.S.C. § 112, First Paragraph, Enablement Rejections

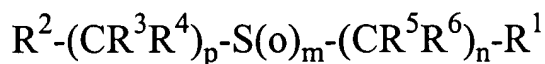
Reconsideration is requested of the rejection of claims 1, 2, 22, 25, and 31-32 under 35 U.S.C. § 112, first paragraph. The Office has asserted that these claims are not sufficiently enabled by the specification.

Claim 1 is directed toward a method to treat a herpetoviridae infection in a subject by administering to the subject a sulfur-containing compound. The sulfur-containing compound, as recited in claim 1, inhibits **both** a (H⁺/K⁺) ATPase and a herpetoviridae protease.

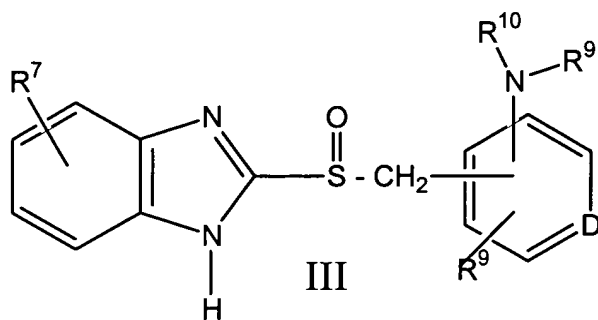
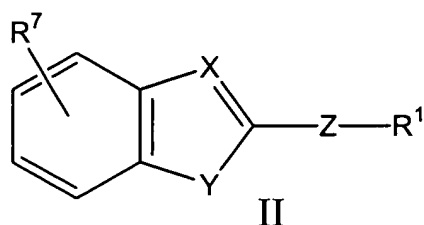
The standard for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation.¹ In this case, the specification coupled with information generally known in the art, fully enables a person of ordinary skill to identify and prepare sulfur-containing compounds that inhibit both a (H⁺/K⁺) ATPase and a herpetoviridae protease for use in the method of claim 1 **without undue experimentation**. Applicants again reiterate that the specification details numerous embodiments of sulfur-containing compounds that may be employed in the

¹U.S. v. Teletronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988).

method of claim 1. According to the specification, the sulfur-containing compound may be a compound having any of the following general formulas I², II³, or III⁴:



I



The specification also details well over 300 examples of specific compounds having formula I, II or III.⁵ In addition, the specification discloses five general reaction schemes that may be utilized to prepare compounds having formula I, II, or III⁶ along with over 100 examples of compounds that were made following the steps of one of the five general schemes. Moreover, the specification discloses biological data showing the ability of tested compounds to inhibit **both** a (H⁺/K⁺) ATPase and a herpetoviridae

²Compounds having formula I are detailed on pages 6-24 of the specification.

³Compounds having formula II are detailed on pages 24-39 of the specification.

⁴Compounds having formula II are detailed on pages 39-45 of the specification.

⁵See pages 11-24 of the specification.

⁶General reaction schemes one through five are disclosed on pages 56-64 of the specification. Examples of specific compounds prepared by one of these reaction schemes are disclosed on pages 71-129 of the specification.

protease⁷ as well as detailed assays that fully enable a skilled artisan to determine the ability of any particular compound to inhibit **both** a (H⁺/K⁺) ATPase and a herpetoviridae protease⁸.

Applicants are aware that there are a large number of sulfur-containing compounds. However, the method of claim 1 requires the use of a sulfur-containing compound that inhibits both a (H⁺/K⁺) ATPase and a herpetoviridae protease. One of the ordinary skill in the art can readily determine whether a particular sulfur-containing compound possesses both of the above-mentioned inhibitory activities. For example, the specification describes assays that can be used to test the ability of a compound to inhibit a (H⁺/K⁺) ATPase (see, e.g., pages 11-137) and to inhibit a herpetoviridae protease (see, e.g., pages 137-144). Accordingly, even though a skilled artisan may have to perform assays to determine whether a particular sulfur-containing compound satisfies the criteria of claim 1, such experimentation is routine considering the amount of information provided in the specification regarding the assays. According to MPEP §2164.06, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Thus, selecting an appropriate sulfur-containing compound was clearly described in a manner so as to enable a skilled artisan to make and use the method of claim 1 without undue experimentation.

According to the Office, however, claim 1 is not enabled because an undue amount of experimentation would be required to determine whether a particular sulfur-containing compound could be used for treating a herpetoviridae infection in light of the existence of "millions of sulfur containing compounds...which may or may not treat

⁷Assays evaluating the ability of compounds to inhibit a (H⁺/K⁺) ATPase are disclosed on pages 111-137 of the specification. Assays evaluating the ability of compounds to inhibit a protease are detailed on pages 137-144 of the specification.

⁸Assays evaluating the ability of compounds to inhibit a (H⁺/K⁺) ATPase are disclosed on pages 111-137 of the specification. Assays evaluating the ability of compounds to inhibit a protease are detailed on pages 137-144 of the specification.

herpetoviridae infection."⁹ In arriving at this conclusion, the Office relied on In re Wands.¹⁰ In the Wands case, the claim at issue required using an antibody "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M^{-1} ."¹¹ The Federal Circuit discussed several of the relevant factors, and concluded that "undue experimentation would not be required to practice the invention."¹² Contrary to the Office's assertion, however, Wands supports the conclusion that claim 1 is sufficiently enabled. Each of the factors considered by the Federal Circuit in the Wands case is discussed below.¹³

With regard to the factor of "the amount of direction provided by the inventor," the Federal Circuit concluded that Wands provided "significant guidance and direction on how to practice the invention and present[ed] working examples." The Wands patent (4,879,219) is 18 columns long, including two columns of claims. Applicants' present specification is 144 pages long prior to the claims, including 88 pages (56-144) devoted to synthesis, working examples, and screening. The present specification provides five general schemes for the preparation of sulfur-containing compounds having formulas I, II or III generally, as well as for the preparation of particular classes of compounds within the scope of each formula, in addition to intermediates useful in their preparation and the specification discloses over 100 examples illustrating the preparation of particular species within the scope of formula I, II or III. One skilled in the art, equipped with the detailed disclosure of the instant specification, and familiar with basic synthetic organic chemistry, could readily adapt the synthetic schemes and examples described in the specification to prepare, select and test compounds within the scope of claim 1. Such adaptation is clearly within the abilities of one skilled in the

⁹See Paper 10 at page 2.

¹⁰In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

¹¹*Id.*, at 8 USPQ2d p. 1402.

¹²*Id.*, at 8 USPQ2d p. 1406.

¹³The factors include: nature of the invention, breadth of the claims, guidance in the specification, working examples, state of the art, predictability of the art, the quantity of experimentation necessary.

art, and while some experimentation may be needed, such experimentation could be routinely performed by the skilled artisan, i.e., the adaptation could be accomplished without undue experimentation.

With regard to "the level of skill," the Federal Circuit stated "There was a high level of skill in the art at the time when the application was filed."¹⁴ In the present situation, the level of skill of pharmaceutical chemists in the field of chemical synthesis is similarly high.

With regard to "the nature of the invention," the Federal Circuit in Wands stated that

the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Similarly in the present case, the nature of the invention requires reasonable screening, and pharmaceutical chemists in the field of chemical synthesis are prepared to screen sulfur-containing compounds falling within the claim scope .

With regard to "working examples," Wands conducted just ten fusion experiments to produce hybridomas having the required binding affinity¹⁵, and carried out the entire synthesis and screening procedure just three times.¹⁶ The present specification provides 111 detailed working examples of syntheses and tested 57 compounds for their ability to inhibit a (H⁺/K⁺) ATPase¹⁷ and 17 compounds for their ability to inhibit a herpetoviridae protease¹⁸ . This cannot fairly be deemed to favor a finding of non-enablement.

¹⁴In re Wands, 8 USPQ2d 1406.

¹⁵*Id.*, at 8 USPQ2d 1405.

¹⁶*Id.*, at 8 USPQ2d 1407.

¹⁷See Table 1 at pages 134-136 of the specification.

¹⁸See Table 2 at page 142 of the specification.

With regard to "state of the art," the state of the art is especially well developed in the fields of chemical synthesis and screening for pharmaceutical activity.

With regard to the "breadth of the claims," the Federal Circuit noted that of 143 candidate antibodies produced by Wands, his testing of just nine and proving the required activity of just four, not even considering countless others which Wands did not make, was sufficient to support claims of the following breadth: "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M^{-1} ."¹⁹ This breadth, deemed acceptable, is much broader than a claim limited to those antibodies that Wands either produced or tested. Against this background, the breadth of claim 1 is reasonable in light of the 144 pages of explanatory specification including 88 pages devoted to synthesis, working examples, detailed biological screening of synthesized compounds, and detailed assays that fully enable a skilled artisan to screen putative sulfur containing compounds for their ability to inhibit both a (H^+/K^+) ATPase and a herpetoviridae protease .

With regard to the "level of predictability," the Federal Circuit in Wands noted that viewing the data as proposed by the Board, only four of 143 of Wands' hybridomas, or 2.8% of those produced (not even considering those not produced), were proven to have the activity required by the claims.²⁰ In the present specification many more candidates than four were tested (i.e., 57), and screening according to the procedures in the specification is well within the ordinary skill in the art.

With regard to the "quantity of experimentation," in Wands nine of 143 hybridomas were tested, and four were determined to have the required activity. This left 130+ hybridomas produced untested, as well as countless others not even produced. The present applicants should similarly not be precluded from patent protection on the basis they have left a considerable quantity of compounds untested, because, as stated by the Board:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance

¹⁹In re Wands, at 8 USPQ2d 1405.

²⁰*Id.*, at 8 USPQ2d 1405.

with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.²¹

Patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention.²²

Furthermore, as stated in *In re Angstadt and Griffin*, 190 USPQ 218:

In the instant case, appellants' invention is the use of a complex catalyst comprising a hexaalkylphosphoramidate and a transition metal salt to catalyze the oxidation of secondary or tertiary alkylaromatic hydrocarbons to form hydroperoxides. Appellants have, in fact, provided those skilled in the art with a large but finite list of transitional metal salts from which to choose in preparing such a complex catalyst. Appellants have actually carried out 40 runs using various transition metal salts and hexaalkylphosphoramidates. If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for directions how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed. The process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention. One skilled in the art would merely have to substitute the correct mass of a transition metal salt for the transition metal salts disclosed in appellants' 40 runs. Thus, we have no basis for concluding that persons skilled in this art, armed with the specification and its 40 working examples, would not easily be able to determine which catalyst complexes within the scope of the claims work to produce hydroperoxides and which do not. (Emphasis added.)

Applicants turn the Examiner's attention to the use of broad terms, such as a complex catalyst comprising a hexaalkylphosphoramidate and a transition metal salt, a number of which were disclosed in the 40 working examples. Similarly, in the present application, Applicants have listed over 300 exemplary compounds in the specification, and have provided 111 working examples describing the synthesis of various compounds. Applicants have also tested 57 compounds for the inhibition of (H⁺/K⁺) ATPase and 17 compounds for the ability to inhibit a herpetoviridae protease. In addition, the

²¹ Ex parte Forman, 230 U.S.P.Q. 546, 547 (BPAI 1986); see also MPEP 2164.06.

²² In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).

processes for testing sulfur-containing compounds for the ability to inhibit a (H⁺/K⁺) ATPase and a herpetoviridae protease are not complicated and there is no indication that "special equipment or unusual reaction conditions" must be provided in order to practice the present invention.

It was further stated in *In re Angstadt and Griffin*, 190 USPQ 218 that:

Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. (Original emphasis.)

Thus, the disclosure of about 300 exemplary compounds and over 100 working examples should be more than sufficient to enable claim 1.

For all of the foregoing reasons, the Office has failed to establish that claim 1 is not sufficiently enabled. Moreover, claims 2, 22, 25, 31, 32, and 33 which depend from claim 1, are likewise enabled for all of the reasons detailed regarding claim 1. Furthermore, claim 33 has been rewritten to relate to a method of treating a subject with a therapeutically effective amount of a **sulfur-containing benzimidazole compound**, wherein the compound is an inhibitor of a (H⁺/K⁺) ATPase and an inhibitor of a herpetoviridae protease. In view of the telephonic interview with the Examiner (discussed above), Applicants believe that the amendment to claim 33 overcomes the Office's rejection under 35 U.S.C. § 112.

II. 35 U.S.C. § 102 (b) Rejection

Reconsideration is requested of the rejection of claims 1, 2, 22, 25 and 31-39 under 35 U.S.C. § 102(b) as anticipated by EP 0 407 217 (EP '217).

Claim 1 is directed toward a method to treat a herpetoviridae infection in a subject by administering to the subject a sulfur-containing compound. The sulfur-containing compound, as recited in claim 1, inhibits **both** a (H⁺/K⁺) ATPase and a

herpetoviridae protease.

EP '217 generally discloses a class of compounds that are said to have antiviral activity, antiinflammatory activity, and that are platelet activating factor inhibitors.

Nowhere does EP '217 disclose or suggest sulfur-containing compounds that are dual inhibitors of **a (H⁺/K⁺) ATPase** and **a herpetoviridae protease**, as required by claim 1. A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference.²³ Because EP '217 does not disclose every element of claim 1, the reference does not anticipate claim 1.

The Office, however, asserts that EP '217 discloses "treatment of herpetoviridae infection using sulfur containing compounds" and that inhibition of a (H⁺/K⁺) ATPase and a herpetoviridae protease by the compounds disclosed in EP '217, and in particular example 30, "is inherent."²⁴

To properly support a determination of inherency, as a matter of Patent Office practice, it is incumbent on the Office to first provide rationale or evidence tending to show inherency.²⁵ In establishing this rationale or evidence, the Examiner must provide a basis in fact and/or technical reasoning to support the determination that the allegedly inherent characteristic **necessarily** flows from the teaching of the cited art.²⁶ Furthermore, the mere fact that a certain characteristic may be present in the prior art is not sufficient to establish the inherency of that characteristic. Only after this initial burden of proof has been met by the Office, does the burden shift to the Applicant.

Against the backdrop of this legal standard, the Office has not properly supported its determination of inherency. The Office has merely stated "inasmuch as the structure of the compounds are similar [i.e., the compounds disclosed in the present invention and Example 30 of EP '217], the disease is the same, it will be expected that the compounds will have the same mechanism, i.e., inhibition of herpetoviridae protease."²⁷ No rationale or evidence has been provided by the Office to support this

²³Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP § 2131.

²⁴Paper 10 at page 4.

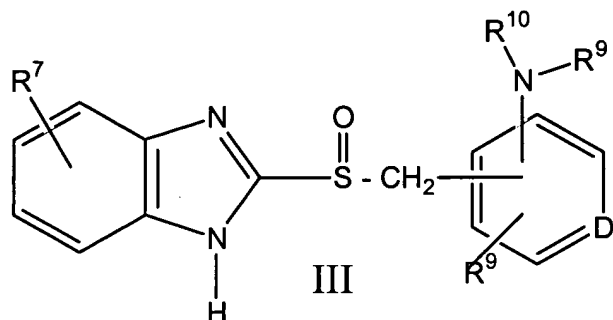
²⁵See MPEP § 2112.

²⁶Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

²⁷Paper 10 at page 5.

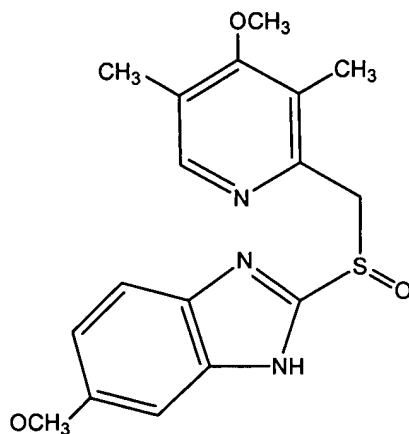
conclusion.

The cited art of record, in fact, casts doubt upon the conclusions relied upon by the Office in arriving at its inherency rejection in view of the known structure and function of several disclosed prior art compounds. One sulfur containing compound detailed in the present specification as suitable for use in the method of claim 1 and cited by the Office, is a benzimidazole compound having the following general formula III:



Compounds having formula III are disclosed in the present specification as inhibitors of **both a (H^+/K^+) ATPase and a herpetoviridae protease.**

Lindberg et al.,²⁸ a reference cited by the Office in its obviousness rejection, disclose a gastric acid secretion inhibitor, omeprazole, having the formula:

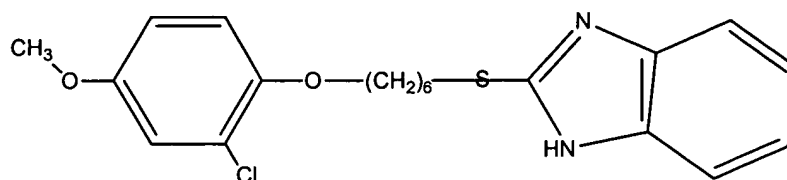


Lindberg et al. disclose that omeprazole is a (H^+/K^+) ATPase inhibitor. But nowhere

²⁸Lindberg et al., (1987) TIPS 8:399-402.

does Lindberg et al. disclose that omeprazole is an inhibitor of a herpetoviridae protease. To the contrary, Table 2 in the present specification details results comparing the ability of a number compounds that are (H^+/K^+) ATPase inhibitors to inhibit assemblin (i.e., a serine viral protease). One of the compounds tested was omeprazole and it was found to have 0% assemblin inhibition activity.²⁹ Despite being structurally similar to benzimidazole compounds of the current invention having formula III, omeprazole does not have the same function.

The compound disclosed by EP '217 in Example 30 (i.e., the compound referenced by the Office in its inherency rejection) has the following structure:



The compounds disclosed in EP '217 are said to have antiviral activity, antiinflammatory activity, and are said to be platelet activating factor inhibitors. Nowhere, does EP '217 disclose or suggest that any disclosed compound (including Example 30) has the ability to inhibit both a (H^+/K^+) ATPase and a herpetoviridae protease. The Office, as detailed above, has stated that because Example 30 is structurally similar to benzimidazole compounds having formula III "it will be expected that the compounds will have the same mechanism, i.e., inhibition of herpetoviridae protease."³⁰ In light of the fact that omeprazole is structurally more similar to benzimidazole compounds having formula III than is the compound of Example 30, and yet does not inhibit assemblin (i.e., a serine viral protease), serious doubt is cast upon the Office's conclusion that the compound of Example 30 inherently has the same function as benzimidazole compounds having formula III.

For the foregoing reasons, the Office has failed to establish that claim 1 is anticipated by the disclosure of EP '217. Moreover, claims 2, 22, 25, 31, 32, and new

²⁹See page 142 of the specification.

³⁰Paper 10 at page 5.

claim 33, which depend from claim 1, are patentable over the cited art for all of the reasons identified for claim 1 and by reason of the additional requirements that they introduce.

III. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1-2, 22, 25 and 31-39 under 35 U.S.C. § 103(a) in view of EP 0 407 217 ('217) and Lindberg et al.³¹

Lindberg et al. disclose a class of gastric acid secretion inhibitors, omeprazole, which prevent gastric acid secretion by inhibiting the gastric H^+/K^+ ATPase.³² According to Lindberg et al., the primary use of the compounds is for the treatment of **gastric ulcers**.³³ Lindberg et al. do not disclose or suggest a method to treat **herpetoviridae infection**. Lindberg et al. also do not disclose or suggest sulfur-containing compounds that are dual inhibitors of **a (H^+/K^+) ATPase** and **a herpetoviridae protease**, as required by claim 1.

EP '217 generally discloses a class of compounds that are said to have antiviral activity, antiinflammatory activity, and that are platelet activating factor inhibitors. Nowhere does EP '217 disclose or suggest sulfur-containing compounds that are dual inhibitors of **a (H^+/K^+) ATPase** and **a herpetoviridae protease**, as required by claim 1.

In the absence of any disclosure of these elements of the method defined in claim 1, a *prima facie* case for obviousness is lacking.

According to the Office, it would have been *prima facie* obvious "to use the Lindberg et al. compounds for treating herpes infection, as taught by EP '217, because the latter reference expressly teach that the benzimidazole class of compounds containing sulfur are known to treat herpes."³⁴ There is no motivation, either express or implied in the references themselves or offered by the Office as to why a skilled artisan would have made the Office's proposed substitution. Accordingly, a skilled artisan empowered with the cited art cannot fairly be deemed to have been motivated to

³¹Lindberg et al., (1987) TIPS 8:399-402.

³²Lindberg et al. see abstract.

³³*Id.*

³⁴Paper 10 at page 5.

substitute the anti secretory, sulfur-containing compounds disclosed by Lindberg et al. for the antiviral, sulfur-containing compounds disclosed in EP '217 to treat a herpetoviridae infection. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

Moreover, as set-forth in II. above, Table 2 in the present specification details results comparing the ability of a number of compounds that are (H⁺/K⁺) ATPase inhibitors to inhibit assemblin (i.e., a serine viral protease). One of the compounds tested was omeprazole (i.e., the compound disclosed by Lindberg et al.) and it was found to have 0% assemblin inhibition activity.³⁵ If a skilled artisan had made the Office's proposed substitution, accordingly, they would not have arrived at the method of claim 1.

The Office, however, asserts that it is not relevant that the cited art make no mention of treatment of infection caused by herpetoviridae virus infection because "discovery of a new benefit for an old process does not render the old process patentable" based upon the theory of inherency.³⁶ For all of the reasons detailed in II. above, the Office has not sufficiently supported a determination of inherency. Additionally, Applicant's have not simply discovered a new property inherent to a process disclosed in the cited art. Claim 1 is directed toward a method to treat **herpetoviridae infection** by administering a compound that is a dual inhibitor of a (H⁺/K⁺) ATPase and a herpetoviridae protease. Nowhere does the cited art, alone or taken together, disclose or suggest a method to treat herpetoviridae infection in a subject by administering a compound that is a dual inhibitor of a (H⁺/K⁺) ATPase and a herpetoviridae protease.

In light of the foregoing reasons, the Office has failed to establish that claim 1 is *prima facie* obvious in view of EP '217 and Lindberg et al. Moreover, claims 2, 22, 25, 31, 32, and new claim 33, which depend from claim 1, are likewise patentable over these references for the reasons stated with respect to claim 1 and by reason of the additional requirements that they introduce.

³⁵See page 142 of the specification.

³⁶See Paper 10 at page 5.

V. Conclusion

In light of the foregoing, Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

Applicants request an extension of time to and including May 28, 2004 for filing a response to the above-mentioned Office action. A check in the amount of \$110.00 in payment of the applicable extension fee is enclosed. The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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